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Short report

Effect of using fidaxomicin on recurrent *Clostridium difficile* infection

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SUMMARY

Fidaxomicin is a macrocyclic antibiotic licensed for treating *Clostridium difficile* infection (CDI). In the UK, fidaxomicin is often reserved for severe CDI or recurrences. At Queen Elizabeth Hospital Birmingham, all courses of fidaxomicin during 2017/2018 were reviewed. Thirty-eight patients received fidaxomicin, of which 64% responded to treatment when fidaxomicin was given during the first episode of mild CDI. Conversely, all patients with recurrent CDI failed treatment with fidaxomicin. There were mixed results for the use of fidaxomicin for severe CDI, with only 42% of patients responding. These results suggest that fidaxomicin is best suited as a treatment for mild CDI during a patient's first episode.

Introduction

Clostridium difficile infection (CDI) causes a range of symptoms ranging from mild diarrhoea to life-threatening pseudomembranous colitis [1–4]. The majority of patients experience a single episode of infection; however, despite treatment, some develop further episodes termed 'recurrent CDI' (rCDI) [1]. It is estimated that, following initial resolution of symptoms, rCDI occurs in 20–30% of patients. Fidaxomicin is a macrocyclic antibiotic licensed for treating CDI. Fidaxomicin has been shown to have comparable clinical cure when compared with vancomycin [1,2]. In the UK, vancomycin and fidaxomicin are generally reserved for severe CDI or for subsequent recurrences [5]. There are limited data on fidaxomicin and its effect/usefulness for the treatment of rCDI and severe CDI [5]. Recently, Enoch *et al.* reviewed all episodes of fidaxomicin use at an English hospital in order to assess patient outcome data [5]. They described fidaxomicin use in 15 patients with rCDI, and concluded that although fidaxomicin was well tolerated, the utility of fidaxomicin at this stage of infection is unclear [5]. At Queen Elizabeth Hospital Birmingham (QEHB), the treatment algorithm includes first-line therapy with metronidazole for patients with mild-to-moderate CDI, vancomycin for relapsed or severe CDI, followed by fidaxomicin in the event of treatment failure or faecal microbiota transplant (FMT) after two recurrences/treatment failures [6]. During 2017/2018, 38 patients received fidaxomicin for CDI at QEHB. Similar to Enoch *et al.*, the authors reviewed all episodes of fidaxomicin prescription in order to assess patient outcome data [5].

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Methods

Setting

QEHB, part of University Hospitals Birmingham NHS Foundation Trust, is a tertiary referral teaching hospital in Birmingham, UK that provides clinical services to over one million patients every year.

C. difficile testing

In line with national guidance, an algorithmic approach to identifying CDI is undertaken at QEHB [4,7–9]. A three-stage algorithm is employed [7–9]. Briefly, any patient with at least one episode of unexplained diarrhoea has their faecal specimen tested for CDI. The CDI testing algorithm consists of an initial screening step using a Premier glutamate dehydrogenase (GDH) enzyme immunoassay (EIA) (Meridian Bioscience, Cincinnati, OH, USA), followed by a nucleic acid amplification test (NAAT) (Xpert *C. difficile*; Cepheid, Sunnyville, CA, USA) for GDH-positive samples alone [7]. All samples testing GDH- and NAAT-positive have a Premier Toxins A and B EIA (Meridian Bioscience) [7].

Study design and definitions

A single-centre observational retrospective cohort study was undertaken. All patients aged ≥18 years commenced on fidaxomicin between April 2017 and March 2018 were reviewed for clinical response to CDI treatment. All 38 patients who were positive by GDH and NAAT, and treated with fidaxomicin, between April 2017 and March 2018 were included in the study. The Bristol Stool Chart and clinical features were analysed based on the daily assessment infection severity tool (DAISY), as described previously [6]. DAISY was also used to define mild, mild-to-moderate and severe forms of CDI [6]. In addition, details of patient outcome (at end of therapy and at 30 and 90 days after cessation of therapy: resolution of diarrhoea, ongoing diarrhoea or death) were collected. Time until diarrhoea resolution was defined in accordance with Enoch *et al.* [5].

Recurrent CDI

Recurrent CDI was defined as the return of diarrhoea (at least one episode of unexplained diarrhoea) within 28 days of a previous CDI episode, and the presence of a positive test result for toxigenic *C. difficile* by GDH and NAAT [6,7].

Treatment failure

Treatment failure was defined as cases where failure to respond to treatment resulted in a change of CDI therapy of the patient [9,10].

Clinical data collection

Patient data collected at the time of a positive result included: patient demographics (age, sex), markers of CDI severity (white cell count, C-reactive protein, serum creatinine, serum albumin, temperature, stool frequency) and mortality (one-month and 3-month all-cause mortality).

Results

Fidaxomicin treatment

During 2017/2018, there were 356 toxin-positive results in 293 patients. Twenty-one percent of these patients had more than one positive toxin result, including 10 patients who had three or more positive toxin results. All 38 patients treated with fidaxomicin received the recommended course of 200 mg twice daily, administered orally for 10 days. Treatment failure with fidaxomicin was declared after the recommended course and duration. Sixteen patients had mild-to-moderate CDI, 12 patients had severe CDI and 10 patients had rCDI (Table I); no patients received fidaxomicin as first-line therapy. Whereas the response rates to fidaxomicin in patients with mild-to-moderate and severe CDI were 63% and 42%, respectively, no patient with rCDI responded. The rCDI patients were prescribed fidaxomicin an average of 4.3 months after their first CDI (fidaxomicin prescription ranging from one to 10 months after the first CDI episode). Five of the rCDI patients had mild symptoms, four had mild-to-moderate CDI and one had severe CDI. Fidaxomicin was well tolerated with no adverse effects documented for any patient.

First episode of *C. difficile*

Twenty of the 38 patients received fidaxomicin during their first episode of CDI where symptoms did not resolve on first-line treatment with metronidazole and/or vancomycin. Eleven of the patients received metronidazole as first-line treatment, which was escalated to vancomycin. Eleven (55%) of these 20 patients responded to fidaxomicin (Table I). Time to resolution of symptoms ranged from four to 10 days (median eight days). Patients with mild-to-moderate CDI were more likely to

Table I
Treatment outcomes at the end of 30 days with patients treated at Queen Elizabeth Hospital Birmingham with fidaxomicin in 2017/2018

	All treatment				Treated within first episode			
	Responded	Failed	Total	Percentage	Responded	Failed	Total	Percentage
Mild CDI	10	6	16	63	9	5	14	64
Severe CDI	5	7	12	42	2	4	6	33
Recurrent CDI[a]	0	10	10	0	-	-	-	-
Total	15	23	38	39	11	9	20	55

CDI, *Clostridium difficile* infection.
[a] Of these patients, five had mild CDI, four had mild-to-moderate CDI and one had severe CDI.

respond than patients with severe disease (64% vs 33%). Ten of the 11 patients who responded remained symptom-free at 90 days (the other patient died 60 days after completing therapy of reasons unrelated to CDI).

Discussion

Overall, this work confirms the findings of Enoch *et al.* that there was a poor outcome for patients with rCDI treated with fidaxomicin [5]. In the present study, all patients with rCDI failed treatment with fidaxomicin, whereas Enoch *et al.* reported a 50% failure rate [5]. The present results suggest that fidaxomicin is best suited as a treatment for mild CDI during a patient's first episode, rather than current UK guidance suggesting its use for severe or rCDI [10]. Likewise, a recent systematic review by Bienortas *et al.* suggested that fidaxomicin frequently provides a sustained cure for non-multiple recurrent infections of CDI compared with vancomycin [11]. This is not surprising as fidaxomicin may persist on *C. difficile* spores, whereas vancomycin does not [12]. This persistence could prevent subsequent growth and toxin production *in vitro*, having implications on spore viability, thereby impacting rCDI rates [12]. Current guidelines suggest that vancomycin and fidaxomicin are of equal efficacy for treating first recurrences of CDI [10]. They recommend oral vancomycin or fidaxomicin for second (or subsequent) recurrences of CDI, citing evidence from Cornely *et al.* and Louie *et al.* where success was seen using fidaxomicin to treat rCDI [13,14]. This is in contrast to the present data and the results of Enoch *et al.* [5]. Confounders cannot be ruled out as a reason for these discrepancies, and further work with larger numbers of patients is needed; however, it should be noted that none of the rCDI patients in the present study were immunosuppressed. The authors have previously reported a lower rCDI rate (16%) than the national average of 25%, and suggested that this may be due to the novel ways of managing CDI at the study hospital [6]. In particular, the use of DAISY to monitor patients' CDI progression and tailor CDI treatment accordingly may select for a particularly recalcitrant group of rCDI patients [6].

In conclusion, this study and the findings of Enoch *et al.* [5] support the use of FMT for the treatment of rCDI, as per the recent joint British Society of Gastroenterology and Healthcare Infection Society guidance [15]. The authors have previously reported a success rate up to 90% for treating rCDI with FMT [7]. With the cost of a 10-day course of fidaxomicin being approximately £1350, compared with £650 for FMT, it is suggested that fidaxomicin should mainly be considered as a treatment option for non-multiply recurrent CDI.

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Conflict of interest statement
None declared.

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